# SIOP#PODC adapted risk stratification and treatment guidelines: Recommendations for neuroblastoma in low# and middle#income settings

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# CLINICAL PRACTICE GUIDELINES
# SIOP-PODC Adapted Risk Stratification and Treatment Guidelines: Recommendations for Neuroblastoma in Low- and Middle-Income Settings

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Neuroblastoma is the most common extracranial solid tumor in childhood in high-income countries (HIC), where consistent treatment approaches based on clinical and tumor biological risk stratification have steadily improved outcomes. However, in low- and middle- income countries (LMIC), suboptimal diagnosis, risk stratification, and treatment may occur due to limited resources and unavailable infrastructure. The clinical practice guidelines outlined in this manuscript are based on current published evidence and expert opinions. Standard risk stratification and treatment explicitly adapted to graduated resource settings can improve outcomes for children with neuroblastoma by reducing preventable toxic death and relapse. Pediatr Blood Cancer 2015;62:1305–1316.


**Key words:** diagnosis; low income countries; MYCN; Neuroblastoma; resource limited countries; treatment

## INTRODUCTION

Neuroblastoma is the most common extracranial solid tumor in childhood in high-income countries (HIC), where it accounts for 10% of pediatric cancers [1]. However, in low- and middle- income countries (LMIC) with population-based registries, it accounts for only 1–3% of cancers, and in most LMIC its true incidence is unknown [2–4]. The limited available data suggest that in LMIC, late diagnosis, lack of access to accurate staging, risk stratification, optimal treatment, and abandonment lead to survival rates much lower than those in HIC [3,5–9]. With the Pediatric Oncology in Developing Countries (PODC) committee of the International Society of Pediatric Oncology (SIOP) working group for adapted treatment regimens, we developed these recommendations for adapted management of neuroblastoma.

This manuscript focuses on neuroblastoma, since general principles of adapted therapy have been previously reported [10–13]. Optimizing treatment in LMIC at centers with variable capabilities and infrastructure requires adapting diagnostic methods, risk stratification, and therapy for children with neuroblastoma based on available resources [10–13]. In Table I, we defined each setting based on the minimal required resources to facilitate appropriate diagnosis and risk-stratified, intensity-adapted treatment. We have used the terminology ''Setting 1'' to represent centers with minimal resources, but with access to care and treatment with curative intent, while ''Setting 4'' represents centers with state-of-the-art diagnostic and treatment capability for high-risk neuroblastoma. Many countries, especially low-income countries (LIC), have extreme heterogeneity in resources available where some privately-funded centers may represent Setting 3, while nearby institutions may be Setting 1. A consistent approach to diagnosis and treatment that is adapted to local conditions and resource availability will improve the care of children in LMIC.

## METHODS

A Global Neuroblastoma Network (GNN) subcommittee of pediatric oncologists from LMIC and HIC reviewed published evidence about treatment strategies for low-risk, intermediate-risk, and high-risk neuroblastoma and applied these strategies during weekly online Global Neuroblastoma Network (GNN) case discussions held via www.Cure4Kids.org. The subcommittee consensus recommendations are based on review of published evidence (using PubMed ®) for neuroblastoma diagnostics, risk assessments, prognostic markers, and treatment strategies combined with expert opinion about neuroblastoma and healthcare delivery in LMIC. The draft was reviewed by peers in HIC and LMIC and presented to a broad group of pediatric solid tumor experts via web conferences of the SIOP PODC working group on adapted treatment regimens, the annual SIOP meeting, and the GNN weekly online multidisciplinary conferences [14].

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.



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**TABLE I. Resource Settings for Neuroblastoma Diagnosis, Staging, and Risk Stratification**

| | Setting 1 | Setting 2 | Setting 3 | Setting 4 |
|---|---|---|---|---|
| Diagnosis | History, Physical examination,<br>Histology of small round blue cell tumor or bone marrow metastases<br>Urinary catecholamines (if available) | | | |
| Staging | CXR and skeletal survey,<br>Abdominal ultrasound,<br>Bilateral BM aspirate & biopsy | CT neck/chest/abdomen/pelvis<br>$^{99m}$Tc-bone Scan<br>Bilateral BM aspirate & biopsy | CT neck/chest/abdomen/pelvis<br>$^{123}$I- MIBG or $^{18}$FDG-PET<br>MRI head or spine if involved<br>Bilateral BM aspirate & biopsy | CT scan neck/chest/abdomen/pelvis<br>$^{123}$I- MIBG or $^{18}$FDG-PET,<br>MRI head or spine if involved<br>Bilateral BM & biopsy |
| Laboratory | CBC, liver enzymes, LDH,<br>ferritin, creatinine, urinalysis | CBC, liver enzymes, LDH, ferritin,<br>creatinine, urinalysis<br>Urine HVA/VMA | CBC, liver enzymes, LDH, ferritin,<br>creatinine, urinalysis<br>Urine HVA/ VMA,<br>Tumor lysis labs if INSS 4<br>(electrolytes, Ca Mg PO4, uric acid) | CBC, liver enzymes, LDH, ferritin,<br>creatinine, urinalysis<br>Urine HVA/ VMA,<br>Tumor lysis labs if INSS 4<br>(electrolytes, Ca Mg PO4, uric acid) |
| Pathology | H&E stain | H&E stain<br>IHC | H&E stain, IHC<br>INPC classification (if available)<br>(differentiation grade, MKI)<br>*MYCN* | H&E stain, IHC<br>INPC classification<br>*MYCN*, DNA Ploidy<br>segmental chromosome abnormalities |
| Infrastructure | Nursing, Inpatient Hospital<br>Access to RBC or whole blood | Nursing, Inpatient hospital<br>Access to RBC & Platelets<br>Pediatric Surgeon<br>Family Housing<br>Intensive Monitoring Capabilities | Nursing, Inpatient Hospital<br>Rapid Access to all Blood Products Pediatric Surgeon<br>Family Housing<br>Pediatric ICU<br>Isolation and Transplant Facility | Nursing, Inpatient Hospital<br>Rapid Access to all Blood Products Pediatric Surgeon<br>Family Housing<br>Pediatric ICU<br>Isolation and Transplant Facility |
| Therapeutics | Antibiotics<br>Standard Chemotherapy | Antibiotics<br>Standard Chemotherapy<br>Radiation Therapy | Antibiotics<br>Standard Chemotherapy<br>Radiation Therapy<br>Transplant Conditioning Agents<br>Isotretinoin | Antibiotics<br>Standard Chemotherapy<br>Radiation Therapy<br>Transplant Conditioning Agents<br>Isotretinoin, Anti-GD2 antibody |

CT, computerized tomography; CBC, complete blood count; LDH, lactic dehydrogenase; H&E, hematoxylin and eosin stain; IHC, immunohistochemistry; RBC, red blood cell; HVA, homovanillic acid; VMA, vannilylmandelic acid; $^{123}$I- MIBG, metaiodobenzylguanidine; FDG-PET, fluorodeoxyglucose positron emission tomography; MRI, magnetic resonance imaging.

## DIAGNOSIS

The diagnosis of neuroblastoma is based on pathology with immunohistochemistry (IHC) complemented by urine catecholamines. In all settings, physical examination, basic laboratory, radiographic, and pathologic evaluation should be performed (Table I). Neuroblastoma should be suspected in children with cervical, mediastinal, paraspinal, abdominal or pelvic masses, and the diagnosis made by either biopsy of the primary tumor or by identification of characteristic tumor cells in the bone marrow. The presence of hypertension may suggest neuroblastoma or Wilms tumor. Elevated urine catecholamines, including urine homovanillic acid (HVA), vannilylmandelic acid (VMA), strongly suggest the diagnosis, and is helpful to distinguish among small round blue cell tumors [15]. Conversely, if urine catecholamines are not available or are non-diagnostic, neuroblastoma can be differentiated from other small round blue cell tumors using IHC staining for tyrosine hydroxylase, CD56, and synaptophysin. Alternative diagnosis should be considered for IHC positive staining for leukocyte common antigen CD45 in lymphoma, CD99 in Ewing sarcoma, and desmin and myogenin in rhabdomyosarcoma [16]. In Setting 1, IHC is usually not available, and the treating doctor will have to rely on a combination of the pathologic appearance and typical clinical features (e.g., age at diagnosis, symptoms, sites of disease, sites of metastases, lack of response to glucocorticoid therapy).

## STAGING AND RESPONSE EVALUATION

Accurate staging and response evaluation are essential for determining treatment and prognosis (Table I). In all settings, bilateral bone marrow aspirate and biopsy should be performed to detect bone marrow metastases, which occur in 70% of metastatic neuroblastoma patients [17]. Radiologic and surgical staging depend on locally available resources: Advance imaging, including magnetic resonance imaging (MRI), $^{123}$I-metaiodobenzylguanidine ($^{123}$I-mIBG) scans, and $^{18}$FDG-PET have increased the accuracy of diagnosis and staging and facilitate local control with surgery and radiotherapy, but due to high cost, are inconsistently available in LMIC [18,19]. Surgical staging of the primary tumor is according to the International Neuroblastoma Staging System (INSS-Supplemental Appendix I) [20]. The recent International Neuroblastoma Risk Group (INRG-Supplemental Appendix I) staging system is a simpler, radiologic staging, which is not influenced by degree of resection [21].

### Setting 1

Staging and response assessment depend on imaging studies and bilateral bone marrow biopsy with simple hematoxylin and eosin staining to document presence of disease (Table I). Plain radiographs and abdominal ultrasound can document the extent of thoracic and abdominal disease [22], but are suboptimal for staging and pre-operative planning due to their lack of sensitivity to detect small metastatic lesions in lymph nodes or lungs. Evaluation for bone disease should include bone radiographs (e.g., a skeletal survey), with the understanding that plain radiographs are less sensitive (26% lesions identified) than bone scan (59% lesions identified) to detect skeletal involvement [23,24].

### Setting 2

Computerized tomography (CT) of neck, chest, abdomen, and pelvis with intravenous contrast combined with $^{99m}$Tc phosphonate nuclear imaging provides greater sensitivity of anatomic location, associated radiologic risk factors for surgery, and metastasis (Table I). CT is more sensitive for bone involvement than plain radiographs. If spinal involvement is suspected, magnetic resonance imaging (MRI), if available, should be obtained to assess invasion of the neural foramina and spinal cord compression.

### Setting 3

In Setting 3, the neuroblastoma staging and risk classification should include CT of neck, chest, abdomen, and pelvis with intravenous contrast; MRI of sites with suspected spinal involvement and sites where tumor extent is not well defined by CT; and $^{123}$I- mIBG scans, or $^{18}$FDG-PET (Table I). $^{123}$I- mIBG, which is taken up via the norepinephrine transporter in 90% of patients with neuroblastoma [19] is the most sensitive and specific test for metastatic disease in bone or soft tissue. An $^{18}$FDG-PET scan is also sensitive, but less specific than mIBG for neuroblastoma but can be used in patients whose tumors are $^{123}$I- mIBG negative or when $^{123}$I- mIBG scans are unavailable [18].

## RISK STRATIFICATION

In the past two decades, risk stratification using clinical and tumor biological features has facilitated intensity-adjusted neuroblastoma therapy with resultant improvements in outcomes and decreased complications in HIC [22,25–28]. Established prognostic markers utilized over the past two decades include clinical features such as stage, age, serum lactate dehydrogenase (LDH), serum ferritin; tumor histological classification; and tumor biologic features of *MYCN* gene amplification status, DNA ploidy and segmental chromosomal aberrations [29–31].

Histologic classification according to International Neuroblastoma Pathology Classification (INPC) could be helpful in all settings to guide risk stratification [15]. Unfortunately, INPC has been underutilized in LMIC due to shortages of trained pathologists familiar with pediatric malignancy and INPC. Fluorescent in situ hybridization (FISH) or RT-PCR for tumor *MYCN* gene amplification is desirable, but are most essential in risk stratification for children with stage 4 tumor in patients $<$18 months of age, and for all stage 3 tumors. DNA ploidy is most helpful in infants without *MYCN* amplified disease, who have stage 4 or 4 S disease, as patients with diploid tumors have significantly lower survival, and may require more intensive therapy [32,33].

### Prognosis

In HIC, children with localized disease and favorable biology tumors (INSS 1, 2, and 4 S or INRG L1, and MS) have an overall survival (OS) of 96% with surgery alone, or in some cases observation only [20–22,31,34,35]. In the intermediate risk group, comprising of infants with metastatic disease or infants and children with unresectable (INSS 3 or INRG L2) disease without tumor *MYCN* amplification, the OS remains greater than 90% when treated with 3–6 months of outpatient chemotherapy of moderate intensity [26]. Yet in LMIC, survival rates even for localized disease is usually lower [5–7] perhaps due to inaccurate staging or risk stratification. Lack of access to biologic risk classification may lead to over-treatment and higher risk of death from aggressive surgical, toxicity, or treatment abandonment. Treating high-risk disease, comprised mainly of children $>$18 months with stage 3 and 4

disease and any stage with *MYCN* amplified tumors is challenging even in HIC, with OS of 40% using modern protocols in settings with excellent supportive care [36–40]. Due to economic, social, and health system factors, high-risk patients typically form a greater proportion of patients diagnosed with neuroblastoma in LMIC than HIC. In LMIC, especially in Setting 1 centers, high risk patient are often not treated with curative intent, since expected survival rates would be <10% [5,6].

## Adapted Risk Stratification

Guidelines for risk stratification are shown in Table II. Age and stage continue to be the strongest clinical prognostic factors for neuroblastoma. Age <18 months implies favorable disease, even in the presence of metastases, provided there is no tumor *MYCN* gene amplification [31,41]. In Setting 3, where INPC classification may be performed, toddlers age 12–18 months with stage 4 disease with Unfavorable Histology (if available) and/or diploidy/hypodiploidy should be considered to have high-risk disease even without *MYCN* amplification. However, toddlers with stage 3 disease without *MYCN* amplification should still be treated on the intermediate risk protocol, as the benefit of transplant is not clearly defined [42]. Children ≥18 months of age with stage 4 disease should be treated as high-risk, without further need for biologic or clinical markers [31].

One significant limitation in LMIC is the inability to assess *MYCN* amplification in some centers, despite the fact that it is present in approximately 25% of patients [43] and is critical to differentiate between intermediate and high-risk disease for patients <18 months with stage 4 disease, and for all patients with stage 3 disease [31]. Although *MYCN* amplification in stage 1, 2, and 4 S tumors could potentially change the risk group, it is uncommon in this group [25]. When *MYCN* assessment is not available, we would consider use of serum LDH and serum ferritin as surrogate markers for *MYCN* amplification in INSS stage 3 and 4 disease [44]. In Children's Cancer Group Study 3891, 70 eligible newly diagnosed patients with Evans stage 3 disease were evaluated for ferritin as a prognostic marker, demonstrating 5-year EFS $38 \pm 9\%$ for patients with ferritin >143 ng/ml versus $78 \pm 8\%$ for those with ferritin <143 ng/ml [42,45]. A review of INRG database identified 1483 INSS stage 3 patients, of which ferritin was known in 666 patients, and LDH in 959 patients. Five-year EFS associated with ferritin <96 ng/ml versus ≥96 ng/ml was $77 \pm 3\%$ versus $61 \pm 4\%$, respectively ($P = <0.0001$), while the 5-year EFS for patients with LDH <580 U/L versus ≥580 U/L was $78 \pm 2\%$ versus $67 \pm 3\%$, respectively ($P = <0.0001$) [42]. Therefore, any patient with stage 3 disease and those <18 months with stage 4 disease whose LDH and/or ferritin exceed this threshold may be stratified as high-risk [33,42,45–47]. If we had to determine a single marker, LDH would be arbitrarily used, as that has the most literature support. The reported threshold at which elevated LDH serves as a prognostic marker varies from >580 IU/L to >1000 IU/L [42,48]; therefore, we recommend the intermediate level of 750 IU/L to intensify therapy in LMIC when *MYCN* status is unknown. The reported threshold at which elevated ferritin has been shown to affect outcome has varied, from >92 ng/ml to >142 ng/ml [31,48,49]; therefore we recommend considering a pre-treatment ferritin ≥120 ng/ml to intensify therapy in LMIC when *MYCN* status is unknown. For both ferritin and LDH, we chose to use an intermediate rather than the highest value as the proposed threshold, acknowledging differences in laboratory ranges while noting that the largest INRG analysis used the lower value. LDH and ferritin assessments are of uncertain prognostic significance in patients with INSS 1, 2, or 4 S tumors, and therefore not recommended for changing the risk category in those patients [22,25,28,31,34].

# TREATMENT GUIDELINES

Treatment guidelines according to risk group and setting are outlined in Table II.

## Low Risk Disease

In patients with INSS 1 and 2 tumors, the outcome is excellent, with >95% 3 year OS [27,50]. Regardless of setting, surgical resection is sufficient for asymptomatic patients whose tumor is largely (>50%) resected, even if some residual tumor remains. Patients with tumor resection can be monitored without further therapy, with ultrasound or CT every 3 months for the 1st year and then every 6 months until 2 years after diagnosis [27]. Perinatal adrenal neuroblastoma (Very Low Risk—VLR) patients, with small adrenal masses detected before birth or within the first six post-natal months, have an especially favorable outcome with >95% 4 year OS, without any surgical or medical intervention [35]. We recommend monitoring these patients with ultrasonography and physical exam every 6–8 weeks, until the mass resolves, or until significant growth warrants surgical resection. Occasionally, these patients will progress to INSS 4 S, but they can be safely observed as long as they remain asymptomatic [51,52].

Infants with stage 4 S asymptomatic disease have an overall 5 years survival 100% for those patients that did not require chemotherapy [51]. For patients with symptomatic stage 4 S neuroblastoma with hepatic dysfunction, coagulopathy, respiratory compromise, or renal impairment, we recommend treatment with intermediate risk therapy. Infants younger than 3 months with hepatomegaly even without symptoms deserve prompt intermediate risk treatment until symptoms abate due to the higher risk of death at this age [33,51].

## Intermediate Risk Disease

There have been significant advances in the therapies for children with intermediate risk neuroblastoma, allowing de-intensification of therapy while maintaining survival. Children with stage 3 intermediate risk neuroblastoma or infants with stage 4 were treated in the 1990s with cisplatin, etoposide, doxorubicin, and cyclophosphamide over 9 months, with a 4-year EFS of 100% for favorable stage 3 [53] and 3-year EFS >93% for infants with INSS 4, *MYCN*-Non amplified disease [54]. The poor prognostic indicators identified in the infant group were diploid and/or *MYCN*-amplified tumors [32,55]. A French cooperative trial showed that INSS 3 infants without *MYCN* gene amplification had a $94 \pm 5\%$ EFS with moderate-intensity chemotherapy [56]. A large INRG report showed that patients with INSS stage 3 tumors without *MYCN* amplification had an 81% 5-year EFS [42].

Therapy has since been modified to shorten the course of treatment, substitute carboplatin for cisplatin, and decrease the cumulative doses of active agents by 60% in an effort to decrease toxicities, hospital stay, and costs, while maintaining survival outcomes, with 88% 3-year EFS and 96% OS [26]. In settings where

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**TABLE II. Adapted Risk Stratification and Treatment Assignment for Neuroblastoma in LMIC**

| INSS | Initial Status | Risk Group | Age (yr) | LDH | Ferritin | MYCN | Rx S-1 | Rx S-2 | Rx S-3 |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Resection[a] | Low | 0.5-21 | any | any | any | Resection | Resection | Resection |
| 1 | Observation | VLR | <0.5 | any | any | any | Observation | Observation | Observation |
| 2A/2B | Resection ≥50%, asymptomatic | Low | any | any[b] | any[b] | NA/Unknown[b] | Observation | Observation | Observation |
| 2A/2B | Resection ≥50%, symptomatic | Intermediate | any | any[b] | any[b] | NA/Unk[b] | IR[c] x 4 cycles-80%[c] | IR[c] x 4 cycles-100% | IR[c] x 4 cycles-100% |
| 2A/2B | Resection <50% | Intermediate | any | any[b] | any[b] | NA/Unk[b] | IR[c] x 4 cycles-80% | IR[c] x 4 cycles-100% | IR[c] x 4 cycles-100% |
| 2A/2B | Any resection | High | any | any | any | A | HR-1 or IR[c] x 8 cycles-80% | HR-2 | HR-3 |
| 3 | | Intermediate | <1.5 | <750 | <120 | NA/Unk | IR[c] x 4 cycles-80% | IR[c] x 4 cycles-100% | IR[c] x 4 cycles-100% |
| 3 | | Intermediate | ≥1.5 | <750 | <120 | NA/Unk | IR[c] x 8 cycles-80% | IR[c] x 8 cycles-100% | IR[c] x 8 cycles-100% |
| 3 | | High | any | ≥750[b] | ≥120[b] | A/Unk | HR -1 or IR[c] x 8 cycles-80% | HR-2 | HR-3 |
| 4 | | High | <1.5 | ≥750[b] | ≥120[b] | A/Unk | HR -1 or IR[c] x 8 cycles-80% | HR-2 | HR-3[f] |
| 4 | | Intermediate[d] | <1.5 | <750 | <120 | NA/Unk | IR[c] x 4 cycles-80% | IR[c] x 4 cycles-100% | IR[c] x 4 cycles-100% |
| 4 | | High | ≥1.5 | any | any | any | HR -1 or IR[c]-8 cycles 80% | HR-2 | HR-3 |
| 4S | Asymptomatic | Low | <1 | <750 | <120 | NA/Unk | Observation | Observation | Observation |
| 4S | Symptomatic[e] | Intermediate | <1 | <750 | <120 | NA/Unk | IR[c] x 4 cycles-80% | IR[c] x 4cycles-100% | IR[c] x 4 cycles-100% |
| 4S | Asymptomatic or symptomatic | High | <1 | any | any | A | IR[c] x 8 cycles-80% | HR-2 | HR-3 |

VLR, very low risk; LR, low risk; IR, intermediate risk; HR, high risk; A, Amplified; NA, Non-Amplified; Unk, Unknown. [a]in low risk patients (INSS Stage 1 and 2), residual tumor (< 50%) is acceptable, as the outcome remains excellent. [b]If *MYCN* is unavailable for low risk patients, would assume that they are low risk. LDH and ferritin have not been established as prognostic markers in INSS 2, Unavailability of *MYCN* with LDH ≥750 units/L and/or ferritin ≥120 ng/μl in stage 3 and 4 disease, would upstage to high risk approach. [c]IR therapy entails chemotherapy + surgery to achieve tumor response >CR/VGPR/PR. IR will entail a minimum of 4 cycles and upto 8 cycles of intermediate risk therapy per A3961, modified dosing based on respective setting designation. [d]In Setting 3, toddlers age 12–<18 months with stage 4 disease without *MYCN* amplification should be considered high risk if the tumor is unfavorable by INPC, if it is diploid, or if LDH and/or ferritin elevated. [e]Stage 4 S symptomatic patients, inability to obtain biology, consider treatment until symptom resolution, with up to 8 cycles. [f]In a setting (i.e., Setting 3), where the INPC determination may be feasible, it would be helpful to be guided with combination of data for adequate risk stratification.

carboplatin is unavailable or is cost-prohibitive, cisplatin can be an alternative. Table III outlines a well-tolerated intermediate-risk therapy suitable for each setting [26]. We recommend dose reduction as outlined in Table II according to availability of resources given the typically favorable outcome and potential need to conserve blood products.

Aggressive surgery may cause significant morbidity in patients with intermediate risk neuroblastoma. Of 235 children with intermediate risk group on the COG A3961 trial, 28% had surgical complications including major hemorrhage, vascular and renal injuries, and intra-operative need for organ resection [26]. Subsequent pilot investigations showed that intermediate risk patients will often mature without progression despite residual unresected tumor [57]. Given the high survival rate for the intermediate group regardless of resection extent [49], we recommend chemotherapy for 4–8 cycles depending on control of metastases and tumor reduction with conservative surgery performed if needed to achieve >50% primary tumor response. Radiation therapy is not recommended even in the setting of residual disease. Patients can be monitored with ultrasound or CT every 3-months for the 1st year and then every 6 months until 2 years after diagnosis.

## High Risk Disease

Despite numerous advances and multimodal therapies in the treatment of children with neuroblastoma, those with high-risk disease continue to be our greatest challenge. The incorporation of three distinct phases of therapy has improved outcome for high-risk neuroblastoma: intensive induction treatment, myeloablative chemotherapy with autologous hematopoietic stem cell rescue, and treatment of MRD [58–60]. The goal of induction therapy is to achieve maximum reduction of tumor burden, including reduction of metastatic bone marrow, and bone disease within a timeframe that will minimize the risk of developing resistant tumor clones and clinical progression. Subsequently, potentially resistant residual tumor is treated with high-dose myeloablative therapy followed by autologous hematopoietic stem cell transplantation (ASCT), which has been shown to significantly improve EFS [58]. The relapse rate of greater than 40% even after such therapies has led to post-transplant treatment for MRD-positive patients using isotretinoin and monoclonal anti-GD2 antibodies [39,58,59].

Due to the lack of transplant expertise, reduced access to blood products and pheresis, and difficulty supporting patients through the period of myelosuppression, few Setting 1 centers in LMIC have attempted curative treatment of high-risk neuroblastoma, and have commonly prescribed palliative care. Furthermore, the cost of isotretinoin and lack of access to monoclonal anti-GD2 antibody impede effective MRD treatment in some LMIC. However, a coordinated treatment approach based on resource capabilities can improve outcome for these children progressively, and will eventually lead to overall improvement in supportive care and therapy of childhood cancer. We propose a graduated intensity plan for high-risk patients in different LMIC settings (Table IV).

## Induction and Local Control

No single chemotherapy induction regimen has proven to be superior for induction response and EFS in high-risk neuroblastoma. All regimens reported to date employ multi-agent chemotherapy with a platinum agent, alkylator therapy such as cyclophosphamide, topoisomerase therapy, usually with etoposide or less frequently, doxorubicin, and vincristine. Initial reports suggested that increasing dose intensity might improve response rate, but this has not been borne out in single arm trials which all showed response rates from 70 to 80% [39,61–63]. The dose-intensive rapid COJEC [64] did show an improvement in EFS compared in a randomized trial to OPEC–OJEC, though the 3-year EFS of 31% was not better than that reported with other North American and European regimens [40].

Given the increased need for supportive care with more intensive regimens and without significant benefit expected for patients without the option of myeloablative therapy, we have recommended induction regimens in Setting 1 using a regimen with low dose metronomic oral cyclophosphamide 25 mg/m$^2$ daily (max 50 mg) or oral etoposide 50 mg/m$^2$/day for palliation of pain and improvement of quality of life, High Risk Setting 1 (HR-1) [65,66]. An alternate approach non-curative therapy would entail administering 1–2 cycles of intermediate risk chemotherapy and local radiation to the primary tumor bed (dosing per Tables III and V) to allow for some tumor reduction, pain relief and improved quality of life. Aggressive pain management is strongly recommended, as end-of-life bone pain can be significant [67].

For Setting 2, we recommend either the same regimen used for intermediate risk patients, (Table III), for 8 cycles or modified-Pediatric Oncology Group (POG) 9341 induction regimen, (Table IV) [26,36]. For Setting 3, we suggest the modified-POG 9341 induction regimen, which is more intensive than prior French CAdO-PE [68], and has fewer reported acute toxicities than N7 [63] or the SIOPEN rapid COJEC [40]. It optimizes platinum, uses less doxorubicin, and has shorter hospitalization (primarily given in a day hospital) and higher response rate than the CCG 3891 protocol [58]. This protocol is currently being used in Morocco for high-risk patients and has been tolerable in >60 patients without toxic death [69]. An alternative option is to administer the OPEC–OJEC regimen that incorporates more carboplatin but avoids doxorubicin; although response rates are lower than those reported for POG 9341 [40]. Surgery to resect the primary tumor is recommended after the 4th or 5th induction cycle in patients, whose metastases have responded significantly to chemotherapy, including either a complete metastatic response or a partial response (PR) and fewer than six residual bone metastases that might be treated with radiotherapy. In a review of patients with high risk neuroblastoma on the CCG A3891 trial, a statistically significant improvement was noted in patients with stage 4 neuroblastoma achieving complete remission after surgery with a 5 year EFS 26% ± 4% versus 19% ± 3% [70] although there are conflicting evidence as to the benefit of complete resection when radiotherapy is also incorporated [71,72]. Given the minimal likely benefit, we recommend avoiding mutilating surgery likely to risk major complications in LMIC and instead using radiation therapy to control unresectable primary tumor and residual bone metastases.

The decision to proceed to a more intensive consolidation should be based on the response to induction chemotherapy. Multiple analyses of myeloablative regimens show that the outcome is significantly better for patients who have achieved at least a partial response at the end of induction [73], and preferably a good partial response in metastases as manifested by a low MIBG Curie score [74].

**TABLE III. Intermediate Risk Regimen for Setting 1, 2, and for High Risk Setting 2**

| Risk Group | Cycle[a] | Chemotherapy[b] | Dose[c] and Administration |
|---|---|---|---|
| IR 1 | 1 | Carboplatin (D1) | 560 mg/m$^2$ (18 mg/kg) in 125 mL/m$^2$ D5 ½ NS IV over 1 hour day 1 |
| | | Etoposide (D1-3) | 120 mg/m$^2$ (4 mg/kg) in 300 mL/m$^2$ D5 ½ NS IV over 2 hours (maximum concentration 0.4mg/mL) Days 1, 2, 3 immediately after Carboplatin infusion is completed |
| | 2 | Carboplatin (D1) | 560 mg/m$^2$ (18 mg/kg) in 125 mL/m$^2$ D5 ½ NS IV over 1 hour day 1 |
| | | Cyclophosphamide (D1) | 1,000 mg/m$^2$ (33 mg/kg) in 125 mL/m$^2$ D5 ½ NS IV over 1 hour day 1 after Carboplatin |
| | | Doxorubicin (D1) | 30 mg/m$^2$ (1 mg/kg) in 125 mL/m$^2$ D5 ½ NS IV over 15-60 minutes day 1 after cyclophosphamide |
| | 3 | Cyclophosphamide (D1) | 1,000 mg/m$^2$ (33 mg/kg) in 125 mL/m$^2$ D5 ½ NS IV over 1 hour day 1 |
| | | Etoposide (D1-3) | 120 mg/m$^2$ (4 mg/kg) in 300 mL/m$^2$ D5 ½ NS over 2 hours daily days 1,2,3 after cyclophosphamide |
| | 4 | Carboplatin (D1) | 560 mg/m$^2$ (18 mg/kg) in 125 mL/m$^2$ D5 ½ NS IV over 1 hour day 1 |
| | | Etoposide (D1-3) | 120 mg/m$^2$ (4 mg/kg) in 300 mL/m$^2$ D5 ½ NS over 2 hours daily days 1,2,3 after Carboplatin |
| | | Doxorubicin (D1) | 30 mg/m$^2$ (1 mg/kg) in 125 mL/m$^2$ D5 ½ NS IV over 15-60 minutes day 1 after Etoposide |
| | Surgery[d] If feasible | | |
| IR 2 | 5 | Carboplatin (D1) | 560 mg/m$^2$ (18 mg/kg) in 125 mL/m$^2$ D5 ½ NS IV over 1 hour day 1 |
| | | Etoposide (D1-3) | 120 mg/m$^2$ (4 mg/kg) in 300 mL/m$^2$ D5 ½ NS over 2 hours daily days 1,2,3 after Carboplatin |
| | 6 | Carboplatin (D1) | 560 mg/m$^2$ (18 mg/kg) in 125 mL/m$^2$ D5 ½ NS IV over 1 hour day 1 |
| | | Cyclophosphamide (D1) | 1,000 mg/m$^2$ (33 mg/kg) in 125 mL/m$^2$ D5 ½ NS IV over 1 hour day 1 after Carboplatin |
| | | Doxorubicin (D1) | 30 mg/m$^2$ (1 mg/kg) in 125 mL/m$^2$ D5 ½ NS IV over 15-60 minutes day 1 after Cyclophosphamide |
| | 7 | Carboplatin (D1) | 560 mg/m$^2$ (18 mg/kg) in 125 mL/m$^2$ D5 ½ NS IV over 1 hour day 1 |
| | | Etoposide (D1-3) | 120 mg/m$^2$ (4 mg/kg) in 300 mL/m$^2$ D5 ½ NS over 2 hours daily days 1,2,3 after Carboplatin |
| | 8 | Cyclophosphamide (D1) | 1,000 mg/m$^2$ (33 mg/kg) in 125 mL/m$^2$ D5 ½ NS IV over 1 hour day 1 |
| | | Doxorubicin (D1) | 30 mg/m$^2$ (1 mg/kg) in 125 mL/m$^2$ D5 ½ NS IV over 15-60 minutes day 1 after Cyclophosphamide |
| | Surgery End of treatment | | |
| Follow up q 3 months x 4, q 6 months x 4, then yearly x 2 with physical exam, urinalysis, VMA/HVA, ultrasound | | | |

NS, Normal Saline; IV, intravenous; IR, intermediate risk, Additional Notes: IR1 will be minimum of 4 cycles of intermediate risk therapy per A3961, modified dosing based on respective setting designation. IR2 will be up to 8 cycles of intermediate risk therapy per A3961, modified dosing based on respective setting designation. [a]Cycles are administered at minimum of 3 week intervals and start after absolute neutrophil count is >1000/μl and platelet count is >100,000/μl. Prior to each cycle, CBC, creatinine, electrolytes, ALT, bilirubin, urinalysis. End of therapy CBC, creatinine, ALT, bilirubin, echocardiogram, imaging (based on setting), CT, mIBG (or bone scan). [b]Recommended to prehydrate with D5 ½ normal saline at 125 ml/m$^2$/hr × 2 hr prior to cyclophosphamide cycles and achieve Urine Specific gravity ≤1.010 prior to starting cyclophosphamide; post hydration with D5 ½ normal saline at 125 ml/m$^2$/hr after chemotherapy with 2 hr hydration after carboplatin cycles and 4 hr of hydration after cyclophosphamide containing cycles. [c]Doses are adjusted to mg/kg for infants <10 kg. For Setting 1, it is recommended to reduce the dose so that only 80% of indicated dose is given, to reduce the likelihood of fever and neutropenia or platelet requirements. [d]After 4 cycles, evaluate for surgery, obtain CBC, creatinine, urinalysis CT, mIBG. The goal of therapy is to achieve resolution of metastases and primary tumor response of >50% with chemotherapy and surgery.

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**TABLE IV. Induction Therapy for High-Risk Neuroblastoma in Setting 3[c]**

| Regimen: POG 9341-Modified | Chemotherapy | Dose and Administration |
|---|---|---|
| Course 1 | Cisplatin | 40 mg/m$^2$/dose (1.33 mg/kg)[a] in 125 ml/m$^2$ NS containing 3 g/m$^2$ mannitol, IV over 1 hr, day 1-5 |
| | Etoposide[b] | 100 mg/m$^2$/dose (3.3 mg/kg)[a] BID 250 ml/m$^2$ NS IV over 2 hr, day 1-3 |
| | Hydration | D5 1/2NS + KCl 30 mEq/L + MgSO4 500 mg/L + Ca Gluconate 250 mg/L at 200 mL/m$^2$/hr for 2 hours prior and 6 hours after each dose of Cisplatin |
| Course 2 | Vincristine | 1.5 mg/m$^2$/dose (.05 mg/kg)[a] IV push days 1, 8, 15 |
| | Cyclophosphamide [a] | 1 g/m$^2$/dose (33 mg/kg)[a] IV in 125 mL/m$^2$ D5 ½ NS IV over 1 hour days 1and 2. |
| | Doxorubicin | 60 mg/m$^2$ /dose (2 mg/kg) IV over 15 min day 1 |
| | Hydration[b] | D5 ½ NS IV at 125 ml/m2/hr for 2 hours prior to and 4 hours after each dose of cyclophosphamide |
| Course 3 | Ifosfamide[a] | 2 g/m$^2$/day (66.6 mg/kg)[a] IV over 1 hour Days 1-5 with MESNA 400 mg/m$^2$ (13.3 mg/kg) in 200 ml/m$^2$ D5 1/2 NS. |
| | Etoposide | 75 mg/m$^2$ (2.5 mg/kg)[a] IV/1 hour in 200 ml/m$^2$ D5 1/2 NS days 1-5 |
| | Hydration[b] | Prehydration: D5 ½ NS IV at 125 ml/m2/hr for 2 hours and Post hydration: D5 1/2 NS at 150 ml/m$^2$/hr and MESNA over 15 min at hr 4, 7, 10 on days 1-5. |
| PBSC collection | | |
| Course 4 | Carboplatin | 500 mg/ m$^2$/day (16.7 mg/kg)[a] IV days 1,2 |
| | Etoposide | 75 mg/m$^2$ (2.5 mg/kg)[a] BID IV/1 hour in 200 ml/m$^2$ D5 1/2 NS |
| | Hydration[b] | Post hydration with D5 1/2 NS at 125 ml/m$^2$/hr x 2 hours |
| Course 5 | Cisplatin | 40 mg/m$^2$/dose (1.33 mg/kg)[a] in 125 ml/m$^2$ NS containing 3 g/m$^2$ mannitol, IV over 1 hr, day 1-5 |
| | Etoposide | 100 mg/m$^2$/dose (3.3 mg/kg)[a] BID 250 ml/m$^2$ NS IV over 2 hr, day 1-3 |
| | Hydration[b] | D5 1/2NS + KCl 30 mEq/L + MgSO4 500 mg/L + Ca Gluconate 250 mg/L at 200 mL/m$^2$/hr for 2 hours prior and 6 hours after each dose of Cisplatin |
| Surgery if $\leq$ 5 metastatic sites remaining | | |

NS, Normal Saline; IV, intravenous. [a]Doses are adjusted to mg/kg for infants <10 kg. [b]Achieve Urine Specific gravity $\leq$1.010 prior to starting cyclophosphamide or ifosfamide. Granulocyte colony stimulating factor should be considered 24 hr after completion of chemotherapy and continued until post-nadir ANC >1,500. [c]Zage PE, Kletzel M, Murray K, et al. Outcomes of the POG 9340/9341/9342 trials for children with high-risk neuroblastoma: A report from the Children's Oncology Group. Pediatr Blood Cancer 2008:51(6):747-753.

**TABLE V. Consolidation and MRD Therapy for High Risk Neuroblastoma**

| Setting | Consolidation | Local Radiation | MRD-directed therapy |
|---|---|---|---|
| Setting 1 | Cyclophosphamide 25 mg/m2/day PO or etoposide 50 mg/m2/day PO | 21 Gy to primary tumor and symptomatic metastases[d] | none |
| Setting 2 | Repeat cycles 1-4 of P9341 (Table IV)[a,b,c] | 21 Gy to Primary tumor bed and up to 5 residual bone metastases[d] | Isotretinoin 80 mg/m$^2$/dose PO BID 14 days of each 28 day cycle for 6 cycles |
| Setting 3 | ASCT with busulfan/melphalan (see supplemental Table 1) | 21 Gy to primary tumor bed and up to 5 residual bone metastases[d] | Isotretinoin 80 mg/m$^2$/dose PO BID 14 days of each 28 day cycle for 6 cycles |
| Follow up | End of therapy US or CT of the primary site, bone scan (setting 1,2) or mIBG scan (Setting 3), bone marrow biopsy, urine VMA/HVA, echocardiogram, hearing test (setting 3). After completion of therapy, monitor q 3 months for 2 years then q 6 months for 3 years with US/CT, urine VMA/HVA. | | |

ASCT, Autologous stem cell transplant; US, Ultrasound; CT, Computed tomography; VMA, Vannillylmandelic acid; HVA Homovanillic acid; Gy, Gray. [a]Hydration guidelines: per Table IV. [b]Achieve Urine Specific gravity $\leq$1.010 prior to starting cyclophosphamide or ifosfamide and use hydration guidelines as outlined in Table IV. [c]Granulocyte colony stimulating factor should be considered 24 hr after completion of chemotherapy and continued until post-nadir ANC >1,500. [d]Gross residual disease should receive additional 14.4 Gy boost at the end of consolidation therapy.

## Consolidation

The recommended consolidation for curative intent is myeloablative therapy with ASCT, based on three randomized trials [39,75,76].

Preliminary results from the European SIOP-EN HR NBL-1 randomized phase III trial comparing busulfan and melphalan (Bu/Mel) versus carboplatin, etoposide, and melphalan (CEM) as a preparative regimen for autologous transplant, showed improved survival in patients treated on the Bu/Mel arm [77–79]. Due to its lesser toxicity and apparently better EFS, we recommend that Setting 3 centers with transplant capabilities utilize either BuMel, (Supplemental Appendix II), or consider melphalan alone (180 mg/m$^2$), as this is the active agent that has been the backbone of almost all neuroblastoma transplant regimens, and was successful in the first randomized trial [76]. One caveat for those utilizing the Bu/Mel regimen is the higher risk of sinusoidal obstructive syndrome (SOS), which may be more severe in LMIC where options for potential prophylaxis or treatment such as defibrotide are not readily available [80].

We recommend that high-risk patients in Setting 1 continue on their same palliative chemotherapy used in induction for a total of 12 months. In Setting 2, a tolerable consolidation therapy would be 4 cycles of modified POG 9341 regimen (Table IV), the French CAdO/CE regimen for 2 cycles each [81] or cyclophosphamide/topotecan for 6 cycles at 3–4–week intervals (Supplemental Appendix III) followed by radiation therapy to the primary tumor bed and residual bone metastases [68]. For Setting 3, if resources are available for ASCT, then a peripheral blood stem cell (PBSC) harvest could be performed after 2–5 cycles of induction. An earlier timing of apheresis generally leads to improved feasibility in obtaining sufficient PBSC numbers. If apheresis is not available, autologous bone marrow could be collected and stored providing that metastases have cleared. If resources to conduct ASCT are not available, then a consolidation using outpatient-based cyclophosphamide/topotecan for 6 cycles at 3–4 week intervals should be considered (Supplemental Appendix III), as this combination was successful in obtaining response in 30% of resistant or relapsed patients [82]. An alternative therapy option would be to continue induction therapy (POG 9341) for another 4 cycles. It is reasonable to continue such chemotherapy with curative intent, as there were still >20% EFS for patients treated with intensive consolidation chemotherapy on the randomized CCG protocol [39]. We recommend administration of 21.6 Gy radiation to the primary tumor bed and to residual bone metastases (fewer than six sites) at the end of consolidation phase of therapy [83,84].

## Minimal Residual Disease Therapy

Although myeloablative therapy has improved the outcome, up to 40% of patients will relapse after this therapy. The CCG reported the benefit of treating children after myeloablative therapy with a differentiating agent, isotretinoin, with significant improvement in EFS for all children post consolidation [58]. Isotretinoin for 6 months is recommended in all settings as post-consolidation therapy for patients who have achieved a complete remission (Table V). It is not effective, and not recommended, for patients with gross residual disease. We would urge particular caution before prescribing isotretinoin for women of child-bearing age to review risks and reinforce pregnancy prevention measures, as there is a serious risk of birth defects in exposed pregnancies. Currently, the

anti-GD2 antibody Ch14.18 based trials, which has been shown to further improve outcome, is not commercially available and requires intensive supportive nursing care for administration, thus limiting access in LMIC.

### Recurrent/Progressive Disease and Alternative Regimens

Despite intensive upfront multimodal therapy, over 50% of high-risk neuroblastoma patients continue to relapse. After relapse these patient have poor outcomes with 5-year OS $< 10\%$ [85]. Regimens such as cyclophosphamide combined with topotecan or irinotecan combined with temozolamide have demonstrated response rates for refractory/relapse disease of 32% and 15%, respectively [82,86]. $^{131}$I-mIBG therapy is also effective in relapsed disease, with a 30% response rate, but is available in few LMIC [87]. External beam radiation therapy will often effectively control symptomatic sites of disease [88]. Oral metronomic therapies may be options for palliation for settings without access to camptothecins or temozolomide [66,89]. Localized recurrence, particularly in low and intermediate risk disease, may be salvageable with additional surgery, radiation, and chemotherapy [26,27,90]. The determination of therapy is guided by timing of recurrence, previous therapies received, individual patient factors and preferences of the family and providers, in addition to the resources available within those centers.

## SUPPORTIVE CARE

Ability to care for children with fever and neutropenia is critical in terms of life threatening complications. Therefore aggressive multi-agent therapy should only be given at center capable of ensuring that patients have rapid access to medical care and broad spectrum antibiotic therapy either by providing affordable housing in close proximity to the medical center or at a facility close to patients' home. It is equally important to educate on fever management with handouts provided to patients and families at each visit [13]. For Setting 3, a central venous catheter should deliver intensive therapy and blood products. It is also recommended in Setting 3 that a pediatric intensive care unit is located within the treating center. Ongoing education should be provided for nursing and medical assistants regarding the care of a child with cancer. Red blood cell products and antibiotics should also be readily available in all settings.

## ADVANCING TREATMENT INTENSITY

The optimal intensity of therapy at each institution should be determined based on the center's own toxicity data, including grade 3 or 4 infection, sepsis, renal impairment, and death. Review of relapses may also guide the decision to adjust therapy, since reduction of intensity may produce a modest decrease in toxic death but a larger increase in relapse. HIC currently report toxic death rates below 5% for both induction and consolidation therapies [91]. A toxic death rate $>5\%$ for induction or 10% for consolidation should trigger careful assessment and use of lower treatment intensity if supportive care cannot be improved. Reviewing institutional data on abandonment rates may help guide practices to promote patient adherence.

## CONCLUSION

Risk classification using an adapted approach that takes into consideration limitations in diagnostic imaging and tumor biology allows risk assignment for children with neuroblastoma, regardless of their setting, and selection of feasible and appropriate treatment. This approach does not preclude active efforts to implement the full range of capabilities in every pediatric cancer unit, but can improve outcomes for those patients who must be treated with the current resources.

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## REFERENCES

1. Gurney JG, Davis S, Severson RK, Fang JY, Ross JA, Robison LL. Trends in cancer incidence among children in the US. Cancer 1996;78:532–541.
2. Parkin DM, Stiller CA, Draper GJ, Bieber CA. The international incidence of childhood cancer. Int J Cancer 1988;42:511–520.
3. Stiller CA, Parkin DM. International variations in the incidence of neuroblastoma. Int J Cancer 1992;52:538–543.
4. Magrath I, Steliarova-Foucher E, Epelman S, Ribeiro RC, Harif M, Li CK, Kebudi R, Macfarlane SD, Howard SC. Paediatric cancer in low-income and middle-income countries. Lancet Oncol 2013;14:e104–e116.
5. Lobo-Sanahuja F, Carranza A, Garcia I, Barrantes M, Camacho-Morales A. Neuroblastoma in Costa Rica: The experience with 76 cases treated at the Hospital Nacional de Ninos. Bol Med Hosp Infant Mex 1991;48:426–433.
6. Kitonyi GW, Macharia WM, Mwanda OW, Pamnani R. Clinico-pathologic characteristics and treatment outcomes in children with neuroblastoma at the Kenyatta National Hospital. Nairobi East Afr Med J 2009;86:S39–S46.
7. Hesseling PB, Ankone K, Wessels G, Schneider JW, Du Plessis, Moore L. Neuroblastoma in southern Africa: Epidemiological features, prognostic factors and outcome. Ann Trop Paediatr 1999;19:357–363.
8. Parise IZ, Haddad BR, Cavalli LR, Pianovski MA, Maggio EM, Parise GA, Watanabe FM, Ioshii SO, Rone JD, Caleffe LG, Odone Filho, Figueiredo V. Neuroblastoma in southern Brazil: An 11-year study. J Pediatr Hematol Oncol 2006;28:82–87.
9. Li K, Dong K, Gao J, Yao W, Xiao X, Zheng S. Neuroblastoma management in Chinese children. J Invest Surg 2012;25:86–92.
10. Hunger SP, Sung L, Howard SC. Treatment strategies and regimens of graduated intensity for childhood acute lymphoblastic leukemia in low-income countries: A proposal. Pediatr Blood Cancer 2009;52:559–565.
11. Chantada G, Luna-Fineman S, Sitorus RS, Kruger M, Israels T, Leal-Leal C, Bakhshi S, Qaddoumi I, Abramson DH, Doz F. Committee S-PG-IRGW. SIOP-PODC recommendations for graduated-intensity treatment of retinoblastoma in developing countries. Pediatr Blood Cancer 2013;60:719–727.
12. Israels T, Moreira C, Scanlan T, Molyneux L, Kampondeni S, Hesseling P, Heij H, Borgstein E, Vujanic G, Pritchard-Jones K, Hadley L. SIOP PODC: Clinical guidelines for the management of children with Wilms tumour in a low income setting. Pediatr Blood cancer 2013;60:5–11.
13. Israels T, Renner L, Hendricks M, Hesseling P, Howard S, Molyneux E. RSIOP PODC: Recommendations for supportive care of children with cancer in a low-income setting. Pediatr Blood Cancer 2013;60:899–904.
14. Parikh NWJ, Sholler G, Roberts S, Howard S, Shochat S, Haase G, Borker A, Kurkure P, Sachdeva A, Matthay K. Advancing diagnosis and treatment of neuroblastoma for children In Low income countries (LIC) via web-based tumor board platform. In: Robert Arceci JMD, Ph. D, Peter E, Newburger MD, editors. Auckland, New Zealand: Wiley Periodicals Inc; 2011. p. 733.
15. Shimada H, Ambros IM, Dehner LP, Hata J, Joshi VV, Roald B, Stram DO, Gerbing RB, Lukens JN, Matthay KK, Castleberry RP. The international neuroblastoma pathology classification (the shimada system). Cancer 1999;86:364–372.
16. Sebire NJ, Gibson S, Rampling D, Williams S, Malone M, Ramsay AD. Immunohistochemical findings in embryonal small round cell tumors with molecular diagnostic confirmation. Appl Immunohistochem mol morphol 2005;13:1–5.
17. DuBois SG, Kalika Y, Lukens JN, Brodeur GM, Seeger RC, Atkinson JB, Haase GM, Black CT, Perez C, Shimada H, Gerbing R, Stram DO, Matthay KK. Metastatic sites in stage IV and IVS neuroblastoma correlate with age, tumor biology, and survival. J Pediatr Hematol Oncol 1999;21:181–189.
18. Sharp SE, Shulkin BL, Gelfand MJ, Salisbury S. 123I-MIBG versus 18F-FDG: Which is better, or which can be eliminated? J Nucl Med 2010.
19. Matthay KK, Shulkin B, Ladenstein R, Michon J, Giammarile F, Lewington V, Pearson AD, Cohn SL. Criteria for evaluation of disease extent by (123)I-metaiodobenzylguanidine scans in neuroblastoma: A report for the International Neuroblastoma Risk Group (INRG) task force. Br J Cancer 2010;102:1319–1326.
20. Brodeur GM, Pritchard J, Berthold F, Carlsen NL, Castel V, Castelberry RP, De Bernardi B, Evans AE, Favrot M, Hedborg F. Revisions of the international criteria for neuroblastoma diagnosis, staging, and response to treatment. J Clin Oncol 1993;11:1466–1477.
21. Monclair T, Brodeur GM, Ambros PF, Brisse HJ, Cecchetto G, Holmes K, Kaneko M, London WB, Matthay KK, Nuchtern JG, von Schweinitz D, Simon T, Cohn SL, Pearson AD, Force IT. The International Neuroblastoma Risk Group (INRG) staging system: An INRG Task Force report. J Clin Oncol 2009;27:298–303.
22. De Bernardi B, Mosseri V, Rubie H, Castel V, Foot A, Ladenstein R, Laureys G, Beck-Popovic M, de Lacerda AF, Pearson AD, De Kraker J, Ambros PF, de Rycke Y, Conte M, Bruzzi P, Michon J. Treatment of localised resectable neuroblastoma. Results of the LNESG1 study by the SIOP Europe Neuroblastoma Group. Br J Cancer 2008;99:1027–1033.

23. Howman-Giles RB, Gilday DL, Ash JM. Radionuclide skeletal survey in neuroblastoma. Radiology 1979;131:497–502.
24. Baker M, Siddiqui AR, Provisor A, Cohen MD. Radiographic and scintigraphic skeletal imaging in patients with neuroblastoma: Concise communication. J Nucl Med 1983;24:467–469.
25. Bagatell R, Beck-Popovic M, London WB, Zhang Y, Pearson AD, Matthay KK, Monclair T, Ambros PF, Cohn SL. Significance of MYCN amplification in international neuroblastoma staging system stage 1 and 2 neuroblastoma: A report from the International Neuroblastoma Risk Group database. J Clin Oncol 2009;27:365–370.
26. Baker DL, Schmidt ML, Cohn SL, Maris JM, London WB, Buxton A, Stram D, Castleberry RP, Shimada H, Sandler A, Shamberger RC, Look AT, Reynolds CP, Seeger RC, Matthay KK. Outcome after reduced chemotherapy for intermediate-risk neuroblastoma. N Engl J Med 2010;363:1313–1323.
27. Perez CA, Matthay KK, Atkinson JB, Seeger RC, Shimada H, Haase GM, Stram DO, Gerbing RB, Lukens JN. Biologic variables in the outcome of stages I and II neuroblastoma treated with surgery as primary therapy: A children's cancer group study. J Clin Oncol 2000;18:18–26.
28. Simon T, Spitz R, Faldum A, Hero B, Berthold F. New definition of low-risk neuroblastoma using stage, age, and 1p and MYCN status. J Pediatr Hematol Oncol 2004;26:791–796.
29. Ambros PF, Ambros IM, Brodeur GM, Haber M, Khan J, Nakagawara A, Schleiermacher G, Speleman F, Spitz R, London WB, Cohn SL, Pearson AD, Maris JM. International consensus for neuroblastoma molecular diagnostics: Report from the International Neuroblastoma Risk Group (INRG) Biology Committee. Br J Cancer 2009;100:1471–1482.
30. Schleiermacher G, Mosseri V, London WB, Maris JM, Brodeur GM, Attiyeh E, Haber M, Khan J, Nakagawara A, Speleman F, Noguera R, Tonini GP, Fischer M, Ambros I, Monclair T, Matthay KK, Ambros P, Cohn SL, Pearson AD. Segmental chromosomal alterations have prognostic impact in neuroblastoma: A report from the INRG project. Br J Cancer 2012;107:1418–1422.
31. Cohn SL, Pearson AD, London WB, Monclair T, Ambros PF, Brodeur GM, Faldum A, Hero B, Iehara T, Machin D, Mosseri V, Simon T, Garaventa A, Castel V, Matthay KK. The International Neuroblastoma Risk Group (INRG) classification system: An INRG Task Force report. J Clin Oncol 2009;27:289–297.
32. George RE, London WB, Cohn SL, Maris JM, Kretschmar C, Diller L, Brodeur GM, Castleberry RP, Look AT. Hyperdiploidy plus nonamplified MYCN confers a favorable prognosis in children 12 to 18 months old with disseminated neuroblastoma: A pediatric oncology group study. J Clin Oncol 2005;23:6466–6473.
33. Taggart DR, London WB, Schmidt ML, DuBois SG, Monclair TF, Nakagawara A, De Bernardi B, Ambros PF, Pearson AD, Cohn SL, Matthay KK. Prognostic value of the stage 4S metastatic pattern and tumor biology in patients with metastatic neuroblastoma diagnosed between birth and 18 months of age. J Clin Oncol 2011;29:4358–4364.
34. Strother DR, London WB, Schmidt ML, Brodeur GM, Shimada H, Thorner P, Collins MH, Tagge E, Adkins S, Reynolds CP, Murray K, Lavey RS, Matthay KK, Castleberry R, Maris JM, Cohn SL. Outcome after surgery alone or with restricted use of chemotherapy for patients with low-risk neuroblastoma: Results of children's oncology group study P 9641. J Clin Oncol 2012;30:1842–1848.
35. Nuchtern JG, London WB, Barnewolt CE, Naranjo A, McGrady PW, Geiger JD, Diller L, Schmidt ML, Maris JM, Cohn SL, Shamberger RC. A prospective study of expectant observation as primary therapy for neuroblastoma in young infants: A children's oncology group study. Ann Surg 2012;256:573–580.
36. Zage PE, Kletzel M, Murray K, Marcus R, Castleberry R, Zhang Y, London WB, Kretschmar C. Outcomes of the POG 9340 /9341/9342 trials for children with high-risk neuroblastoma: A report from the children's oncology group. Pediatr Blood Cancer 2008;51:747–753.
37. De Bernardi B, Nicolas B, Boni L, Indolfi P, Carli M, Cordero Di Montezemolo, Donfrancesco L, Pession A, Provenzi A, di Cataldo M, Rizzo A, Tonini A, Dallorso GP, Conte S, Gambini M, Garaventa C, Bonetti A, Zanazzo F, D'Angelo A, Bruzzi P. Disseminated neuroblastoma in children older than one year at diagnosis: Comparable results with three consecutive high-dose protocols adopted by the Italian Co-Operative Group for Neuroblastoma. J Clin Oncol 2003;21:1592–1601.
38. Simon T, Berthold F, Borkhardt A, Kremens B, De Carolis B, Hero B. Treatment and outcomes of patients with relapsed, high-risk neuroblastoma: Results of German trials. Pediatr Blood Cancer 2011;56:578–583.
39. Matthay KK, Reynolds CP, Seeger RC, Shimada H, Adkins ES, Haas-Kogan D, Gerbing RB, London WB, Villablanca JG. Long-term results for children with high-risk neuroblastoma treated on a randomized trial of myeloablative therapy followed by 13-cis-retinoic acid: A children's oncology group study. J Clin Oncol 2009;27:1007–1013.
40. Pearson AD, Pinkerton CR, Lewis IJ, Imeson J, Ellershaw C, Machin D. High-dose rapid and standard induction chemotherapy for patients aged over 1 year with stage 4 neuroblastoma: A randomised trial. Lancet Oncol 2008;9:247–256.
41. Schmidt ML, Lal A, Seeger RC, Maris JM, Shimada H, O'Leary M, Gerbing RB, Matthay KK. Favorable prognosis for patients 12 to 18 months of age with stage 4 nonamplified MYCN neuroblastoma: A children's cancer group study. J Clin Oncol 2005;23:6474–6480.
42. Meany HJ, London WB, Ambros PF, Matthay KK, Monclair T, Simon T, Garaventa A, Berthold F, Nakagawara A, Cohn SL, Pearson AD, Park JR. Significance of clinical and biologic features in Stage 3 neuroblastoma: A report from the International Neuroblastoma Risk Group project. Pediatr Blood Cancer 2014.
43. Castleberry RP, Pritchard J, Ambros P, Berthold F, Brodeur GM, Castel V, Cohn SL, De Bernardi B, Dicks-Mireaux C, Frappaz D, Haase GM, Haber M, Jones DR, Joshi VV, Kaneko M, Kemshead JT, Kogner P, Lee RE, Matthay KK, Michon JM, Monclair R, Roald BR, Seeger RC, Shaw PJ, Shuster JJ. The International Neuroblastoma Risk Groups (INRG): A preliminary report. Eur J Cancer 1997;33:2113–2116.
44. London WMV, Hero B, Park JR, Valteau-Couanet D, Nakagawara A, Berthold F, Matthay KK, Schleiermacher G, Machin D. A neuroblastoma risk classification model for developing countries: A study from the International Neuroblastoma (NB) Risk Group (INRG) Database. Toronto, CA: SIOP; 2014.
45. Park JR, Villablanca JG, London WB, Gerbing RB, Haas-Kogan D, Adkins ES, Attiyeh EF, Maris JM, Seeger RC, Reynolds CP, Matthay KK. Outcome of high-risk stage 3 neuroblastoma with myeloablative therapy and 13-cis-retinoic acid: A report from the Children's Oncology Group. Pediatr Blood Cancer 2009;52:44–50.
46. Shuster JJ, McWilliams NB, Castleberry R, Nitschke R, Smith EI, Altshuler G, Kun L, Brodeur G, Joshi V, Vietti T, Hayes FA. Serum lactate dehydrogenase in childhood neuroblastoma. A Pediatric Oncology Group recursive partitioning study. Am J Clin Oncol 1992;15:295–303.
47. Lau L. Neuroblastoma a single institution's experience with 128 children and an evaluation of clinical and biological prognostic factors. Pediatr Hematol Oncol 2002;19:79–89.
48. Cangemi G, Reggiardo G, Barco S, Barbagallo L, Conte M, D'Angelo P, Bianchi M, Favre C, Galleni B, Melioli G, Haupt R, Garaventa A, Corrias MV. Prognostic value of ferritin, neuron-specific enolase, lactate dehydrogenase, and urinary and plasmatic catecholamine metabolites in children with neuroblastoma. Onco Targets Ther 2012;5:417–423.
49. Hann HW, Evans AE, Siegel SE, Wong KY, Sather H, Dalton A, Hammond D, Seeger RC. Prognostic importance of serum ferritin in patients with Stages III and IV neuroblastoma: The childrens cancer study group experience. Cancer Res 1985;45:2843–2848.
50. Strother D, Shuster JJ, McWilliams N, Nitschke R, Smith EI, Joshi VJ, Kun L, Hayes FA, Castleberry R. Results of pediatric oncology group protocol 8104 for infants with stages D and DS neuroblastoma. J Pediatr Hematol Oncol 1995;17:254–259.
51. Nickerson HJ, Matthay KK, Seeger RC, Brodeur GM, Shimada H, Perez C, Atkinson JB, Selch M, Gerbing RB, Stram DO, Lukens J. Favorable biology and outcome of stage IV-S neuroblastoma with supportive care or minimal therapy: A children's cancer group study. J Clin Oncol 2000;18:477–486.
52. Hero B, Simon T, Spitz R, Ernestus K, Gnekow AK, Scheel-Walter HG, Schwabe D, Schilling FH, Benz-Bohm G, Berthold F. Localized infant neuroblastomas often show spontaneous regression: Results of the prospective trials NB95-S and NB97. J Clin Oncol 2008;26:1504–1510.
53. Matthay KK, Perez C, Seeger RC, Brodeur GM, Shimada H, Atkinson JB, Black CT, Gerbing R, Haase GM, Stram DO, Swift P, Lukens JN. Successful treatment of stage III neuroblastoma based on prospective biologic staging: A children's cancer group study. J Clin Oncol 1998;16:1256–1264.
54. Schmidt ML, Lukens JN, Seeger RC, Brodeur GM, Shimada H, Gerbing RB, Stram DO, Perez C, Haase GM, Matthay KK. Biologic factors determine prognosis in infants with stage IV neuroblastoma: A prospective children's cancer group study. J Clin Oncol 2000;18:1260–1268.
55. Look AT, Hayes FA, Shuster JJ, Douglass EC, Castleberry RP, Bowman LC, Smith EI, Brodeur GM. Clinical relevance of tumor cell ploidy and N-myc gene amplification in childhood neuroblastoma: A pediatric oncology group study. J Clin Oncol 1991;9:581–591.
56. Rubie H, Coze C, Plantaz D, Munzer C, Defachelles AS, Bergeron C, Thomas C, Chastagner P, Valteau-Couanet D, Michon J, Mosseri V, Hartmann O. Localised and unresectable neuroblastoma in infants: Excellent outcome with low-dose primary chemotherapy. Br J Cancer 2003;89:1605–1609.
57. Marachelian A, Shimada H, Sano H, Jackson H, Stein J, Sposto R, Matthay KK, Baker D, Villablanca JG. The significance of serial histopathology in a residual mass for outcome of intermediate risk stage 3 neuroblastoma. Pediatr Blood Cancer 2012;58:675–681.
58. Matthay KK, Villablanca JG, Seeger RC, Stram DO, Harris RE, Ramsay NK, Swift P, Shimada H, Black CT, Brodeur GM, Gerbing RB, Reynolds CP. Treatment of high-risk neuroblastoma with intensive chemotherapy, radiotherapy, autologous bone marrow transplantation, and 13-cis-retinoic acid. Children's Cancer Group N Engl J Med 1999;341:1165–1173.
59. Yu AL, Gilman AL, Ozkaynak MF, London WB, Kreissman SG, Chen HX, Smith M, Anderson B, Villablanca JG, Matthay KK, Shimada H, Grupp SA, Seeger R, Reynolds CP, Buxton A, Reisfeld RA, Gillies SD, Cohn SL, Maris JM, Sondel PM. Anti-GD2 antibody with GM-CSF, interleukin-2, and isotretinoin for neuroblastoma. N Engl J Med 2010;363:1324–1334.
60. Berthold F, Hero B, Kremens B, Handgretinger R, Henze G, Schilling FH, Schrappe M, Simon T, Spix C. Long-term results and risk profiles of patients in five consecutive trials (1979–1997) with stage 4 neuroblastoma over 1 year of age. Cancer Lett 2003;197:11–17.
61. Valteau-Couanet D, Michon J, Boneu A, Rodary C, Perel Y, Bergeron C, Rubie H, Coze C, Plantaz D, Bernard F, Chastagner P, Bouzy J, Hartmann O. Results of induction chemotherapy in children older than 1 year with a stage 4 neuroblastoma treated with the NB 97 French Society of Pediatric Oncology (SFOP) protocol. J Clin Oncol 2005;23:532–540.
62. Granger M, Grupp SA, Kletzel M, Kretschmar C, Naranjo A, London WB, Diller L. Feasibility of a tandem autologous peripheral blood stem cell transplant regimen for high risk neuroblastoma in a cooperative group setting: A pediatric oncology group study: A report from the children's oncology group. Pediatr Blood Cancer 2012;59:902–907.
63. Cheung NK, Kushner BH, LaQuaglia M, Kramer K, Gollamudi S, Heller G, Gerald W, Yeh S, Finn R, Larson SM, Wuest D, Byrnes M, Dantis E, Mora J, Cheung IY, Rosenfield N, Abramson S, O'Reilly RJ. N7: A novel multi–modality therapy of high risk neuroblastoma (NB) in children diagnosed over 1 year of age. Medical Pediatr Oncol 2001;36:227–230.
64. Ladenstein R, Valteau-Couanet D, Brock P, Yaniv I, Castel V, Laureys G, Malis J, Papadakis V, Lacerda A, Ruud E, Kogner P, Garami M, Balwierz W, Schroeder H, Beck-Popovic M, Schreier G, Machin D, Potschger U, Pearson A. Randomized Trial of prophylactic granulocyte colony-stimulating factor during rapid COJEC induction in pediatric patients with high-risk neuroblastoma: The European HR-NBL1/SIOPEN study. J Clin Oncol 2010;28:3516–3524.
65. Russell HV, Groshen SG, Ara T, DeClerck YA, Hawkins R, Jackson HA, Daldrup-Link HE, Marachelian A, Skerjanec A, Park JR, Katzenstein H, Matthay KK, Blaney SM, Villablanca JG. A phase I study of zoledronic acid and low-dose cyclophosphamide in recurrent/refractory neuroblastoma: A new approaches to neuroblastoma therapy (NANT) study. Pediatr Blood Cancer 2011;57:275–282.
66. Robison NJ, Campigotto F, Chi SN, Manley PE, Turner CD, Zimmerman MA, Chordas CA, Werger AM, Allen JC, Goldman S, Rubin JB, Isakoff MS, Pan WJ, Khatib ZA, Comito MA, Bendel AE, Pietrantonio JB, Kondrat L, Hubbs SM, Neuberg DS, Kieran MW. A phase II trial of a multi-agent oral antiangiogenic (metronomic) regimen in children with recurrent or progressive cancer. Pediatr Blood Cancer 2014;61:636–642.
67. Friedrichsdorf SJ. Pain management in children with advanced cancer and during end-of-life care. Pediatr Hematol Oncol 2010;27:257–261.
68. Coze C, Hartmann O, Michon J, Frappaz D, Dusol F, Rubie H, Plouvier E, Leverger G, Bordigoni P, Behar C, Beck D, Mechinaud F, Bergeron C, Plantaz D, Otten J, Zucker JM, Philip T, Bernard JL. NB87 induction protocol for stage 4 neuroblastoma in children over 1 year of age: A report from the French society of pediatric oncology. J Clin Oncol 1997;15:3433–3440.
69. Khattab M, Cherkaoui S, Benmiloud S, ElHoudzi J, Hessissen L, Lam C, Parikh N, Howard S, Matthay. K. Results of an intensive induction protocol for high-risk neuroblastoma in Morocco (HR-NBL-MA-10). Toronto, CA: SIOP; 2014.
70. Adkins ES, Sawin R, Gerbing RB, London WB, Matthay KK, Haase GM. Efficacy of complete resection for high-risk neuroblastoma: A Children's Cancer Group study. J Pediatr Surg 2004;39:931–936.
71. Du L, Liu L, Zhang C, Cai W, Wu Y, Wang J, Lv F. Role of surgery in the treatment of patients with high-risk neuroblastoma who have a poor response to induction chemotherapy. J Pediatr Surg 2014;49:528–533.
72. Simon T, Haberle B, Hero B, von Schweinitz D, Berthold F. Role of surgery in the treatment of patients with stage 4 neuroblastoma age 18 months or older at diagnosis. J Clin Oncol 2013;31:752–758.
73. Schmidt M, Simon T, Hero B, Schicha H, Berthold F. The prognostic impact of functional imaging with (123)I-mIBG in patients with stage 4 neuroblastoma >1 year of age on a high-risk treatment protocol: results of the German Neuroblastoma Trial NB97. Eur J Cancer 2008;44:1552–1558.
74. Yanik GA, Parisi MT, Shulkin BL, Naranjo A, Kreissman SG, London WB, Villablanca JG, Maris JM, Park JR, Cohn SL, McGrady P, Matthay KK. Semiquantitative mIBG scoring as a prognostic indicator in patients with stage 4 neuroblastoma: A report from the children's oncology group. J Nucl Med 2013;54:541–548.
75. Berthold F, Boos J, Burdach S, Erttmann R, Henze G, Hermann J, Klingebiel T, Kremens B, Schilling FH, Schrappe M, Simon T, Hero B. Myeloablative megatherapy with autologous stem-cell rescue versus oral maintenance chemotherapy as consolidation treatment in patients with high-risk neuroblastoma: A randomised controlled trial. Lancet Oncol 2005;6:649–658.
76. Pritchard J, Cotterill SJ, Germond SM, Imeson J, de Kraker J, Jones DR. High dose melphalan in the treatment of advanced neuroblastoma: Results of a randomised trial (ENSG-1) by the European Neuroblastoma Study Group. Pediatr Blood Cancer 2005;44:348–357.
77. Ladenstein RPU, Luksch R, Brock P, Castel V, Yaniv I, Papadakis V, Laureys G, Pearson A, Valteau-Couanet D. Final Results from the HR-NBL1/SIOPEN trial favour Busulphan-Melphalan as Superior Myeloablativ Therapy (MAT) for high risk neuroblastoma. In: Baruchel S, editor. Toronto: Advances in Neuroblastoma Research; 2012.
78. Valteau-Couanet D, Le Deley MC, Bergeron C, Ducassou S, Michon J, Rubie H, Le Teuff G, Coze C, Plantaz D, Sirvent N, Bouzy J, Chastagner P, Hartmann O. Long-term results of the combination of the N7 induction chemotherapy and the busulfan-melphalan high dose chemotherapy. Pediatr Blood Cancer 2014;61:977–981.

79. Soni S, Pai V, Gross TG, Ranalli M. Busulfan and melphalan as consolidation therapy with autologous peripheral blood stem cell transplantation following Children's Oncology Group (COG) induction platform for high-risk neuroblastoma: Early results from a single institution. Pediatr Transplant 2014;18:217–220.
80. Veal GJ, Nguyen L, Paci A, Riggi M, Amiel M, Valteau-Couanet D, Brock P, Ladenstein R, Vassal G. Busulfan pharmacokinetics following intravenous and oral dosing regimens in children receiving high-dose myeloablative chemotherapy for high-risk neuroblastoma as part of the HR-NBL-1/SIOPEN trial. Eur J Cancer 2012.
81. Rubie H, Michon J, Plantaz D, Peyroulet MC, Coze C, Frappaz D, Chastagner P, Baranzelli MC, Mechinaud F, Boutard P, Lutz P, Perel Y, Leverger G, de Lumley L, Millot F, Stephan JL, Margueritte G, Hartmann O. Unresectable localized neuroblastoma: improved survival after primary chemotherapy including carboplatin-etoposide. Neuroblastoma Study Group of the Societe Francaise d'Oncologie Pediatrique (SFOP). Br J Cancer 1998;77:2310–2317.
82. London WB, Frantz CN, Campbell LA, Seeger RC, Brumback BA, Cohn SL, Matthay KK, Castleberry RP, Diller L. Phase II randomized comparison of topotecan plus cyclophosphamide versus topotecan alone in children with recurrent or refractory neuroblastoma: A Children's Oncology Group study. J Clin Oncol 2010;28:3808–3815.
83. Simon T, Hero B, Bongartz R, Schmidt M, Muller RP, Berthold F. Intensified external-beam radiation therapy improves the outcome of stage 4 neuroblastoma in children $>$ 1 year with residual local disease. Strahlentherapie und Onkologie 2006;182:389–394.
84. Wolden SL, Gollamudi SV, Kushner BH, LaQuaglia M, Kramer K, Rosen N, Abramson S, Cheung NV. Local control with multimodality therapy for stage 4 neuroblastoma International. J Rad Oncol Biol Phys 2000;46:969–974.
85. London WB, Castel V, Monclair T, Ambros PF, Pearson AD, Cohn SL, Berthold F, Nakagawara A, Ladenstein RL, Iehara T, Matthay KK. Clinical and biologic features predictive of survival after relapse of neuroblastoma: A report from the International Neuroblastoma Risk Group project. J Clin Oncol 2011;29:3286–3292.
86. Bagatell R, London WB, Wagner LM, Voss SD, Stewart CF, Maris JM, Kretschmar C, Cohn SL. Phase II study of irinotecan and temozolomide in children with relapsed or refractory neuroblastoma: A Children's Oncology Group study. J Clin Oncol 2011;29:208–213.
87. Matthay KK, Yanik G, Messina J, Quach A, Huberty J, Cheng SC, Veatch J, Goldsby R, Brophy P, Kersun LS, Hawkins RA, Maris JM. Phase II study on the effect of disease sites, age, and prior therapy on response to iodine-131-metaiodobenzylguanidine therapy in refractory neuroblastoma. J Clin Oncol 2007;25:1054–1060.
88. Paulino AC. Palliative radiotherapy in children with neuroblastoma. Pediatr Hematol Oncol 2003;20:111–117.
89. Kushner BH, Kramer K, Cheung NK. Oral etoposide for refractory and relapsed neuroblastoma. J Clin Oncol 1999;17:3221–3225.
90. Bagatell R, Rumcheva P, London WB, Cohn SL, Look AT, Brodeur GM, Frantz C, Joshi V, Thorner P, Rao PV, Castleberry R, Bowman LC. Outcomes of children with intermediate-risk neuroblastoma after treatment stratified by MYCN status and tumor cell ploidy. J Clin Oncol 2005;23:8819–8827.
91. Kreissman SG, Seeger RC, Matthay KK, London WB, Sposto R, Grupp SA, Haas-Kogan DA, Laquaglia MP, Yu AL, Diller L, Buxton A, Park JR, Cohn SL, Maris JM, Reynolds CP, Villablanca JG. Purged versus non-purged peripheral blood stem-cell transplantation for high-risk neuroblastoma (COG A 3973): A randomised phase 3 trial. Lancet Oncol 2013;14:999–1008.